

Post-mortem clinical pharmacology

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Clinical pharmacology assumes that deductions can be made about the concentrations of drugs from a knowledge of the pharmacokinetic parameters in an individual; and that the effects are related to the measured concentration. Post-mortem changes render the assumptions of clinical pharmacology largely invalid, and make the interpretation of concentrations measured in post-mortem samples difficult or impossible. Qualitative tests can show the presence of substances that were not present in life, and can fail to detect substances that led to death. Quantitative analysis is subject to error in itself, and because post-mortem concentrations vary in largely unpredictable ways with the site and time of sampling, as a result of the phenomenon of post-mortem redistribution. Consequently, compilations of 'lethal concentrations' are misleading. There is a lack of adequate studies of the true relationship between fatal events and the concentrations that can be measured subsequently, but without such studies, clinical pharmacologists and others should be wary of interpreting post-mortem measurements.

Introduction

Clinical pharmacology is primarily concerned with two aspects of the interaction between drugs and humans: pharmacodynamics and pharmacokinetics. This review considers what can be established of the pharmacodynamics and pharmacokinetics in life from data acquired after death. It is important in forensic pharmacology [1] to be aware of the extent to which post-mortem samples can be interpreted on the basis of the known pharmacology of a drug. Pharmacological assumptions of what can be deduced about the concentrations of drugs from knowledge of the pharmacokinetic parameters in an individual, and how the effects are related to the measured concentration that may be valid during life are often invalid after death. Extrapolation can therefore lead to erroneous, or at least contentious, conclusions. A recent example is the argument over likely effects of intravenous thiopental, administered as part of a lethal cocktail in the execution of prisoners, where the effects are deduced from thiopental concentrations measured post mortem [2, 3]. Previous reviews have examined aspects of the problem of interpreting post-mortem data, often from a specialist viewpoint [4–10]. Here the general problems are systematically reviewed.

Search strategy

The information used to assemble this review comes from a systematic search of EMBASE 1974 to June 2007 for the keywords AUTOPSY#.W..DE. and DRUG-BLOOD-LEVEL.DE. and Medline 1950 to June 2007 for AUTOPSY#.W..MJ. and TISSUE-DISTRIBUTION.DE. Additionally, both were searched for the text words (postmortem OR (post ADJ mortem)) AND (redistribution). Reference lists of retrieved articles and a personal collection of references were also scanned.

Pharmacodynamics

In forensic pharmacology, the pharmacodynamic question asked of a clinical pharmacologist when a person has died is usually 'did a drug cause or contribute to the death?'. The answer is likely to come from a combined analysis of the medical history, including the reported circumstances and manner of death, a consideration of the likely effects of some presumed dose or measured concentration of drug, the role of other drugs and possible pharmacokinetic factors, and the exclusion of other potential causes.

The medical history

A typical medical history may go some way towards demonstrating a causal role for a drug. At the least, the medical history needs to be consistent with the presumed mechanism of death and the pathological findings, and the dose and the corresponding effect need to be plausible. For example, if a naive (non-tolerant) heroin user were observed to lapse into coma and then seen to suffer a respiratory arrest within a few minutes of a large intravenous dose of heroin, then most would postulate a causal link. It might be difficult, on the other hand, to accept a pathologist's assertion that a person died from an anaphylactic reaction to an injected medicine if the reaction occurred hours after the injection.

In considering the role of a drug in causing death, the analysis of events runs from the fact of death, through suspicion of a pharmacological cause, to the reconciliation of the post-mortem pharmacological data with the medical history. The sequence of analysis is unfamiliar to the clinical pharmacologist, who may be more used to administering a specified dose and observing the effect, or, alternatively, may take a history and perform an examination, then make tests in order to diagnose drug-induced disease. Since bias, and sometimes deception, can influence the history obtained after death, accounts documented before death are especially important. A Swiss study has suggested that the medical history plays an important role in interpreting post-mortem data in about 70% of cases [11].

Qualitative post-mortem analysis

A qualitative test is any test that indicates the presence of a substance, without providing accurate information as to the amount. The mere presence of a drug, or its metabolites, in post-mortem tissue can be sufficient to reinforce suspicions of the link between the drug and the death. The conviction in 2000 of the English General Practitioner Dr Harold Shipman for the murder of 15 of his patients rested in part on the sudden demise of a group of otherwise healthy patients, for the most part elderly women, and in part on the detection of morphine in skeletal muscle from the exhumed bodies of a subset of them, in the absence of evidence that they had been prescribed morphine or been in the habit of taking opiates [12]. The post-mortem detection of morphine must have played a significant part in securing a conviction, but was only one of many pieces of evidence. As Pounder has pointed out [12], there was sufficiently strong circumstantial evidence that, for six of the convictions, no pathological or toxicological evidence was added: those victims had been cremated.

However, a positive result from a qualitative test for the presence of a poisonous substance is not sufficient of itself

to establish that the poison caused death, nor is a negative result sufficient to establish that it did not.

False-positive results

Tests can give erroneously positive results in two ways. First, false-positive test results, where the test shows the presence of a substance that is absent, can arise from unsatisfactory or non-specific tests. For example, radioimmunoassays for digoxin can be positive for endogenous digoxin-like substances that accumulate in renal failure, in the absence of any administration of digoxin [13]. A variant of this is the measurement of two closely related substances, where only one is toxic. One example is the analysis of stereo-isomers that are chemically identical but have different biological properties. R-methadone, for example, is a potent opioid, whereas S-methadone is almost inactive but not distinguished from it in standard analyses [14].

Secondly, results can truly indicate the presence of a substance in a sample taken from a dead body even though the substance was not present in the body before death. This can arise by generation of toxic substances after death, or by contamination. The presence of substances generated after death is a particular difficulty in the assessment of ethanol concentrations [15–17], e.g. in the victims of road traffic accidents [18] and in aircrew [19]. Gamma-hydroxybutyrate, a rapidly acting anaesthetic drug of abuse, can also be generated post mortem [20].

Contamination after burial has been advanced as an explanation for the presence of substances such as arsenic and lead that can be present in soil, or in burial containers [21]. Contamination during sampling, e.g. by taking it into a lithium-heparin tube [22], or during analysis, are also important possibilities. Even in life, qualitative analysis of hair for drugs can be misleading unless steps are taken to avoid surface contamination [23].

A safeguard in qualitative analysis is to use more than one analytical method. Clear recommendations exist to reduce the dangers of sample contamination [24]. Cautious interpretation is still required.

False-negative results

False-negative tests are possible. In the celebrated 19th century case of Dr William Palmer, a man called John Parsons Cook died from convulsions, consistent with strychnine poisoning. The prosecution toxicologist, Dr Alfred Swaine Taylor, failed to find strychnine in Cook's body, but argued that this was a false-negative result due to the poor analytical method [25]. Palmer was convicted; it is less likely that this would happen today. Negative results can sometimes be assumed because standard screening tests have shown nothing suspicious. This may be unwise if relevant specific tests have not been conducted. The initial failure to detect polonium in samples from the Russian Alexander Litvinenko, murdered in London in 2006, may

Table 1

Approximate pharmacokinetic values in life and of central : peripheral blood concentrations measured post mortem for a series of drugs of forensic interest

Reference Name	[64, 65] V_{dist} (l kg ⁻¹ bodyweight)	[64, 65] Plasma protein binding (%)	[64, 65] Octanol : water partition coefficient	[64, 65] Log octanol : water partition coefficient	[64, 65] pKa	[8] Central : peripheral concentration ratio
Amitriptyline	14.5	95	87 000	4.94	9.4	3.1
Chloroquine	200	60	42 600	4.63	8.4	3
Chlorpromazine	7	98.5	2 500	3.40	9.3	4
Clomipramine	14.5	97.25	158 500	5.20		1.9
Clonazepam	3	65	260	2.41	1.5	2
Clozapine	1.6	95	1 700	3.23	7.6	2.8
Codeine	3.6	16	4	0.60	8.2	1.8
Desipramine	22.5	90	25	1.40	10.2	2.4
Dextroamphetamine	5	32.5	63	1.80	9.9	2
Diazepam	1.5	97	500	2.70	3.3	1.6
Dosulepin	45	85	630	2.80		3
Flurazepam	4.5	97	200	2.30	8.2	3
Haloperidol	23	92	1 700	3.23	8.3	3.6
Imipramine	21	85	320	2.51	9.5	2
Ketamine	4	35	1 250	3.10	7.5	1.6
Meperidine	4.2	45	500	2.70	8.7	2.1
Midazolam	1.25	96	20 000	4.30	6.2	4
Morphine	2.25	30	0.8	-0.10	8	2.2
Nortriptyline	26.5	92.5	50	1.70	9.7	2.4
Oxazepam	1.35	96.5	160	2.20	1.7	1.9
Oxycodone	3		5	0.70	8.9	3.1
Paroxetine	15.5	95	8 900	3.95	9.9	2.7
Pentazocine	3.75	62.5	100	2.00	8.5	2
Phenytoin	0.6	91.5	320	2.51	8.3	1.4
Promethazine	13.5	84.5	800	2.90	9.1	1.6
Propoxyphene	16	75	16 000	4.20	6.3	3.5
Temazepam	1.4	86	155	2.19	1.6	1.6
Thiopental	2.5	65	710	2.85	7.6	1.9
Trazodone		92	1 600	3.20	6.7	1.6
Triazolam	1.3	17.5	263	2.42	5	2.8
Venlafaxine	7.5	27	2.7	0.43		1.6
Zolpidem	0.54	92.5	7 000	3.85	6.2	2.1

The extent of post-mortem distribution is measured by the central : peripheral concentration ratio, taken from reference [8]. The volume of distribution is taken from [64]. The regression coefficient of central : peripheral concentration ratio on volume of distribution, $r = 0.247$, $P > 0.1$. The octanol : water partition coefficient is taken from [65]. The regression coefficient of central : peripheral concentration ratio on octanol : water partition coefficient, $r = 0.035$, $P > 0.1$.

have stemmed from a false belief that radioactive substances were absent because standard tests for ionizing radiation were negative [26].

Another important cause of negative post-mortem tests is the disappearance of the drug before analysis. This can occur during life, and in some circumstances is likely or inevitable. For example, if a person dies from hypostatic pneumonia days or weeks after an insult that has caused irreversible brain damage, the agent responsible will not generally be found. Paracetamol causes delayed hepatic toxicity that can be fatal. By the time death occurs, paracetamol cannot be detected in blood (although urinary metabolites may be detected). Paraquat concentration falls rapidly after overdose [27]. Paraquat causes pulmonary fibrosis and a sometimes slow and agonising death many weeks after ingestion, when poison will no longer be found in blood samples, although it may be found in tissues [28].

Even if a true-positive test shows the presence of a substance that was present during life, a qualitative test is not of itself sufficient to imply drug-taking. Misleading results can be due to contaminants from innocent sources: small amounts of opiate can be detected in the urine of persons who have eaten poppy-seed cake [29].

There are, therefore, serious difficulties in interpreting qualitative tests on post-mortem samples: both false-positive and false-negative results can occur.

Quantitative post-mortem analysis

One of the central tenets of clinical pharmacology is that the pharmacological action of a drug is determined by its concentration at the site of action. Most drugs used in modern therapy have a therapeutic index sufficiently high that they are efficacious at concentrations lower than

those capable of producing toxicity [30]. The concentration of a drug in the 'sampling compartment' is assumed to relate to the concentration at the site of action, and that concentration in turn is expected to relate to the dose. However, even at steady-state in life, the relationships between dose and plasma concentration, and between plasma concentration and therapeutic or toxic effect, can vary widely from subject to subject. This is true even when samples are taken at specified times after dosing, so as to reduce variability due to differences in absorption. It is common for drug analyses to give results whose accuracy, measured by difference from nominal values of control samples, and whose precision, measured by differences in repeated samples, may have standard deviations of >10% of mean values. Analytical specificity can also be an important issue. It is sufficiently important with immunoassays that results require confirmation. The sensitivity of an assay also needs to be sufficiently great that concentrations likely to have caused harm can be detected.

For most fatalities, assumptions of steady-state before death are invalid, so that greater allowance needs to be made for variability within and between subjects. The 'sampling compartment' is itself usually different after death from in life. For example, almost all post-mortem analysis is performed on whole blood. Most drug assays in samples from living patients are made on plasma or serum, and whole blood is used uncommonly. After death, and in the most favourable circumstances, it is possible to take samples of whole blood flowing from femoral veins: this sample is thought to be least susceptible to post-mortem change. Failing this, blood can be collected from the heart or another central site. For many drugs, there are marked differences between post-mortem concentrations in samples obtained from peripheral and central sites (Table 1), as discussed below [8].

Even in life, the concentration ratio between whole blood and plasma varies from drug to drug. It is 0.5 for phenytoin, and 2 for maprotiline [31]. After death, the composition of body fluids can change, and so does fluid distribution. Sedimentation of red cells under gravity accounts for hypostatic staining, which is a visible manifestation of post-mortem change. In addition, death entrains cell lysis, and putrefaction by endogenous and exogenous bacteria. Variable degrees of sedimentation, coagulation, haemolysis, putrefaction and contamination with tissue fluids can render quantitative analysis of blood unhelpful, and of blood-tinged fluids collected from body cavities meaningless.

Other body fluids and tissues, including stomach content, urine, liver, muscle and fat, are commonly sampled at autopsy. Quantitative analysis has been used to compare concentrations in suspected cases with concentrations in previous cases attributed to poisoning. This approach is potentially misleading in the absence of knowledge of the changes that can occur under different conditions after death and without comparative material

from patients who were taking the relevant drugs but died from other causes.

The lethal dose

In animal studies, death will occur at lower concentrations of a poison in some animals than in others, and this is the basis for experimental determination of the LD_{50} , the dose that is lethal to 50% of a cohort of animals. The fiducial limits (upper and lower confidence bounds) around the LD_{50} are a measure of the dispersion of susceptibility to the poison in the relevant population. No such data exist for human subjects, and so neither lethal doses (nor lethal concentrations) measured before death, nor their dispersion, are known. There are reliable data on human poisoning in life for a few drugs, such as paracetamol [32], where there has been careful study, where there is reasonable assurance that samples are taken after complete absorption, and where either the outcome or a reliable surrogate (liver enzyme elevation) could be observed. There are a number of counter-examples, such as iron salts and possibly aspirin, where the severity of poisoning is poorly correlated with the concentration of the substance in blood even during life.

Extrapolation from post-mortem concentrations to ante-mortem concentrations

There are many uncertainties in back-extrapolation from a concentration found post-mortem to the concentration before death, and from the putative ante-mortem concentration to its possible effects. Nevertheless, attempts have been made to establish acute lethal concentrations [33–36], even if there is some recognition that this is not straightforward [36, 37]. The difficulties are apparent from the quoted ranges for lethal concentrations of, for example, 3,4-methylenedioxymetamphetamine ('ecstasy') ($40\text{--}8500\text{ }\mu\text{g l}^{-1}$) and methadone ($60\text{--}3100\text{ }\mu\text{g l}^{-1}$) in modern data [38]. Milroy and Forrest found values for the lethal concentration of methadone measured in post-mortem blood variously quoted as $220\text{--}3040$; $200\text{--}4500$; $320\text{--}3980$; $1000\text{--}2000$; and $100\text{--}2500$ (intravenously) or $100\text{--}2600\text{ }\mu\text{g l}^{-1}$ (orally); the range in their own series of 111 cases was $84\text{--}2700\text{ }\mu\text{g l}^{-1}$ [39]. In 25 cases where they were able to sample blood both from an arm and from a leg, it is possible to compute the median difference as $72\text{ }\mu\text{mol l}^{-1}$, with an interquartile range for the difference of $20\text{--}200\text{ }\mu\text{mol l}^{-1}$.

Importance of tolerance

For some important drugs, including many oncological drugs and opioids, there is little or no separation between therapeutic and toxic concentrations. The opioids represent one class of drugs where receptor downregulation during chronic therapy shifts concentration–response curves, so that much higher concentrations are required to produce the same effect, whether beneficial or harmful. The same phenomenon is seen with GABA-agonists,

including ethanol. Although the lethal concentration of ethanol has sometimes been reported as 'above 500 milligrams per 100 millilitres' [40], a patient was still talking when her serum ethanol concentration was >1500 mg per 100 ml, three times this 'fatal' value [41]. Jones and Holmgren examined data on 693 deaths from acute alcohol poisoning, and found a Gaussian distribution of post-mortem concentrations, with a mean value of 356 mg per 100 ml [42]. The 95% confidence interval around the mean (calculated from the quoted standard deviation) was between 185 and 526 mg per 100 ml. The lethal concentration was three times higher in some subjects than in others. The corollary is that all interpretation of the pharmacodynamic effects based on concentrations should be placed in the context of the variations in concentration-response relationships and the degree of tolerance.

Another major concern regarding lethal concentrations is that commonly more than one drug is implicated in a fatality. Possible pharmacokinetic and pharmacodynamic interactions between a drug and ethanol or one drug and another make for still greater difficulties in interpretation.

Site-related and time-related differences in post-mortem concentrations

Holt and Benstead observed in 1975 that three post-mortem samples of blood from different sites in one body contained different concentrations of digoxin, and speculated that drug may have been redistributed in the body after death [43]. By 1980, Rouzioux had described in detail two types of post-mortem change that could affect blood concentrations between the moment of death and the time of autopsy [44]. These were degradation of the toxic substance, e.g. by microbial or enzymatic action, as can happen with cyanides; and modification of the equilibrium between blood and tissues. Both exudation from tissue and cellular lysis could contribute to this change in equilibrium, and Rouzioux reported analyses in 10 cases. Eight cases were marked by blood concentrations, measured in post-mortem samples from the left ventricle, between 2.58 and 17.66 higher than during life, whereas two, both due to carbon monoxide poisoning, had concentrations after death about 25–30% lower than in life [44].

The term 'post-mortem redistribution' was used by Koren and MacLeod in the title for their 1985 paper on changes in digoxin concentration after death, based on experiments in the rat [45]. They administered radio-iodine-labelled digoxin to rats 2 h before death. Concentrations measured at death and 12 h afterwards showed a mean heart : blood ratio of 10.6 and 0.9, respectively. They concluded that *ante-mortem digoxin concentrations cannot be reliably inferred on the basis of high post-mortem levels of the drug alone* (emphasis added).

In the 30 years following the observations of Holt and Benstead, a wide range of potential difficulties in interpreting post-mortem concentrations has been uncovered, and the phenomenon of post-mortem redistribution of drugs

has fully justified its description by Pounder and Jones as 'a toxicological nightmare' [7].

Several reviews have considered the factors that can influence the concentration of drug measured post-mortem [7, 10, 46–49]. They can broadly be divided into two processes. First, the drug may remain unaltered, but its distribution in the body changes as the result of transfer across barriers that maintain a concentration gradient in life, notably cellular membranes. The integrity of the barriers is lost after death. This leads to flux of drug from (or, more rarely, to) the gut, the solid organs, the bladder and the alveoli. It is also possible for drug to be gained or lost from the system, e.g. by evaporation or absorption from the environment. Secondly, the drug can be altered as the result of physicochemical change in the post-mortem environment. For example, as pH changes, so the state of ionization of the drug may change. The drug itself can undergo chemical change. Morphine, for example, can be measured as free or total drug, the latter including both the conjugated metabolites morphine-3-glucuronide and morphine-6-glucuronide. Post-mortem hydrolysis increases apparent free morphine concentrations [50].

Transfer across barriers

Drugs taken orally have to be absorbed from the gut into the bloodstream before distribution around the body. Absorption in life depends on the transfer of drug across the intestinal wall, which can be the result of active transport or the consequence of physicochemical diffusion. The active processes cease after death, and the rate and extent of diffusion depend on the permeability of the gut wall, which increases after death. For example, in life ethanol is absorbed from the small intestine rather than the stomach. However, after death the stomach wall becomes permeable to ethanol, which then diffuses into adjacent tissue and blood vessels [51, 52]. Such diffusion through previously impermeable barriers may be most important for small nonpolar molecules [47].

Drug already filtered from the bloodstream into the urine can diffuse from the bladder into femoral venous blood by similar mechanisms: in a single autopsy case, concentrations of diphenhydramine and dihydrocodeine were an order of magnitude higher in the femoral venous blood than in the cardiac blood, and a further order of magnitude higher in the urine than in the femoral venous blood. The authors hypothesized that death occurred after a long period of unconsciousness during which high concentrations of drug accumulated in the bladder [53].

In life, neither drug in the gut nor drug in the urine would form part of the pharmacologically active body burden. If drug is transferred from the gut or the urine into the blood sampled after death, the blood concentrations will be erroneous.

When 3,4-methylenedioxymetamphetamine ('ecstasy') is given intravenously to rabbits, post-mortem concentrations in heart blood rise primarily as a result of redistribu-

tion from lung tissue. The patterns of this post-mortem redistribution of ecstasy depend on whether it is infused into the stomach, the trachea or the oesophagus. Concentrations in heart blood rise markedly after 'supradiaphragmatic' administration, whereas concentrations in gastric contents remain low unless drug is introduced directly into the stomach [54, 55]. These results show that high post-mortem concentrations can come from absorption across the stomach wall; by redistribution from the lungs of drug already absorbed before death; and from absorption of drug in the trachea or oesophagus, as a result of vomiting or reflux. Studies on cadavers support this last view [56].

Redistribution of absorbed drug

An important part of classical pharmacokinetics is an assessment of the extent to which a drug is distributed uniformly or non-uniformly in the body. For example, heparin, absorbed into the bloodstream, remains localized in the bloodstream. By contrast, almost the entire body load of drugs such as amiodarone and chloroquine lies outside the bloodstream. Where the distribution is non-uniform before death, the possibility arises after death that the distribution will become more uniform simply because there will be flow down any concentration gradient from high concentration to lower concentration (and, more generally, along a gradient of chemical potential) [57]. Organs in which drug is concentrated are loci of high concentration, and concentrations in surrounding tissue can be disproportionately affected. The concentration measured in blood, in these circumstances, depends strongly on the sampling site. For example, digoxin is preferentially distributed to cardiac muscle. After death, concentrations in heart blood are substantially higher than those in femoral venous blood, presumably because of redistribution from cardiac muscle into heart blood [43].

Redistribution from the lungs, which act as a reservoir for basic drugs that are also lipophilic [58], such as amitriptyline, chlorpromazine and methadone, is also important. Movement of drug from the lungs into the left ventricle and aorta after death is rapid and results in a significant increase in drug concentrations in samples from these two sites [47, 59].

Where energy-dependent processes maintain concentration gradients during life, major post-mortem shifts are expected. For example, the ratio of potassium concentration inside and outside cells in life is about 40 : 1 maintained by $\text{Na}^+\text{-K}^+$ ATPase. After death, when there is no further renewal of the energy supply and when the integrity of cell membranes is lost, cell walls become freely permeable to potassium ions, and the concentration inside and outside cells tends to equilibrate. In consequence, serum potassium concentration rises from about 3.5 mmol l^{-1} prior to death to 18 mmol l^{-1} at 1 h, and 25 mmol l^{-1} at 24 h after death [60]. Concentrations above approximately 8 mmol l^{-1} in life are commonly fatal, but

clearly the existence of lethal concentrations before death cannot be inferred from finding them post mortem.

Some evidence for preferential distribution during life can remain post mortem. Mangin and Kintz examined the post-mortem concentrations of morphine in human axillary, head and pubic hair, finding the highest concentrations in the last of these [61]. Rather discouragingly, there appears to be no correlation in life between the dose of opiates administered and the resulting concentration in hair [62].

Influence of volume of distribution

The volume of distribution is a measure of the extent to which a drug is distributed outside the bloodstream in life, and can be interpreted as the ratio of the total amount of drug absorbed into the body to the amount of drug in one unit volume of blood (or plasma). The density of the body is approximately 1 kg l^{-1} , so a drug that is uniformly distributed in a person weighing 70 kg will have a volume of distribution of approximately 70 l. Very high *in vivo* volumes of distribution, implying preferential localization outside the bloodstream, have been proposed as a marker of potential post-mortem redistribution [7, 8, 63].

One determinant of volume of distribution of a drug is its lipid solubility, and that can be established by determining the octanol : water partition coefficient, which measures the extent to which the drug enters the hydrophobic octanol phase (Table 1). There are compilations of values in standard texts [64, 65]. For example, sertraline is extremely hydrophobic, with an octanol : partition coefficient of 195 000, and has a volume of distribution of 20 l kg^{-1} (i.e. 1400 l in a 70-kg person); aspirin, which is strongly hydrophilic, with an octanol : water partition coefficient of 0.08, has a volume of distribution of 0.2 l kg^{-1} . There are, however, many deviations from a simple relationship between octanol : water partition coefficient and volume of distribution. Venlafaxine, with a volume of distribution of 7.5 l kg^{-1} , has a partition coefficient of 2.7; warfarin, whose volume of distribution is 0.14 l kg^{-1} , has a partition coefficient of 400. A partial explanation for this is that some entities, such as lithium, are subject to specific, active processes that remove them from the bloodstream. Others, such as warfarin, are preferentially bound to sites outside the circulating blood. A further complicating factor is that, for many drugs, a high proportion of the fraction in circulating blood is bound to plasma proteins, whereas for a few drugs, plasma protein-binding is negligible. Chlorpromazine is >95% protein-bound, whereas atenolol is <5% protein-bound. For highly protein-bound drugs, the plasma proteins act as a reservoir of inactive, but circulating, drug.

The distribution of protein between the circulating blood and interstitial fluid depends on the maintenance of a semipermeable membrane. Changes in membrane permeability after death allow proteins such as albumin to

leak out of the bloodstream into tissues, reducing the concentration of albumin-bound drug in blood [66].

The effect of pH changes on the state of ionization of an ionizable drug can be deduced from the pK_a , i.e. the pH at which the ratio of unprotonated to protonated drug is unity (Table 1). The benzodiazepines clonazepam, oxazepam and temazepam all have pK_a values <2 – the unprotonated form predominates at physiological pH; whereas desipramine, colchicine and propofol all have pK_a values >10 – the protonated form predominates at physiological pH. If the protonated form of a drug is ionized, then the more acidic the medium, the more ionized drug will be present; and *vice versa* if it is the unprotonated form that is ionized.

Because changes in pH lead to changes in the extent of ionization, and because ionized drug is hydrophilic, they also affect octanol : water partition coefficient and protein binding. For example, the partition coefficient of fluoxetine between octanol and water is 11 000, but between octanol and aqueous buffer at pH 7.4 is 66 [65]. Blood pH falls after death, and also sometimes before death, e.g. in patients who undergo prolonged resuscitation, or who die from respiratory or renal failure.

For all these reasons, the physiochemical properties of drugs, which determine their distribution, will not remain constant after death, and calculations based on pharmacokinetic parameters determined in life are bound to be inaccurate. The practice, at one time common in forensic work, of calculating the 'body-burden' of a drug from the post-mortem concentration and the average volume of distribution, determined *in vivo*, should therefore be abandoned.

Relationship between concentrations measured before and after death

The relationship between ante-mortem and post-mortem drug concentrations is clearly critical in making reasoned judgements of the importance of quantitative analyses. There are, however, few human studies that provide direct evidence. The work of Rouzioux, already referred to, determined the ratios between post-mortem and ante-mortem concentration in four cases of imipramine poisoning to be 4.85, 1.39, 9.94 and 7.60; and in two cases of chloroquine poisoning to be 17.66 and 14.6 (the timing of the samples varied considerably among patients) [44]. A later study found post-mortem femoral blood : ante-mortem serum concentrations of amitriptyline in poisoned patients to be 3.6, 4.3 and 12; and of imipramine to be 3.0 and 6.0 [6]. For chloroquine, the ratio between ante-mortem serum concentration and post-mortem peripheral blood concentration was 0.7, whereas the ratio between post-mortem heart blood and peripheral blood concentrations was 2.9 [67]. Elliott found ratios to be between 1.1 and 6.6 for 3,4-methylenedioxymetamphetamine ('ecstasy') and 1.5 and 13.3 for its metabolite 3,4-methylenedioxyamphetamine [68]. A study in which post-mortem peripheral blood was

compared with ante-mortem serum established ratios of 11.7 for dosulepin, 8.3 for propoxyphene, 3.9 for amitriptyline, 2.6 for methadone, 1.9 for propranolol, 1.5 for paracetamol and 1.0 for salicylate in single cases [69]. The post-mortem : ante-mortem ratio was 1.7 in a man who took an unintentional overdose of diltiazem [70]. Flecaïnide, digoxin and sotalol concentrations, but not amiodarone concentrations, rose after death in an 18-year-old man with heart disease who suffered a fatal arrhythmia [71].

Animal experiments have been helpful, but extrapolation to humans is hampered by differences in both anatomy and pharmacology. Studies in which animals have been given substantial doses of drugs and then been examined post mortem confirm that concentrations vary by site and by time for: citalopram [72, 73], 'ecstasy' [54, 55], fluoxetine [74], morphine [75, 76] and paracetamol [8, 77]. Crandall and coworkers used swine to examine the relationship between ante-mortem and post-mortem concentrations of morphine after acute intravenous overdose [78]. Prior to death, mean left ventricular and femoral venous concentrations were similar for free and for total morphine. After death, both ratios were altered. The mean central : peripheral (C : P) blood ratio for free morphine was approximately 0.5 after 30 min, but 1.0 after 120 min; total morphine C : P ratio exceeded 1.0 at five time-points after death, and was <1.0 at four time-points, perhaps because the study did not examine paired samples, and there may have been substantial interanimal variability. Since concentration in blood from central sites and peripheral sites is, or is assumed to be, equal during life, C : P different from unity suggests that changes have taken place after death. For example, redistribution of drug stored in liver, or transfer from the stomach, are likely to influence central concentrations more than peripheral concentrations, and lead to high C : P ratios. The corollary – that a ratio of unity is a sign that the concentration measured post-mortem is equal to the concentration immediately before death – does not have to be true.

Strandberg *et al.* found post-mortem concentrations of morphine in rats that died within 10 min of diamorphine overdose to be nearly 10 times higher in lung tissue than in heart blood, although differences were much less in rats that survived for some hours after overdose [79]. Morphine : metabolite ratios were variable. Large differences in ratios of major morphine metabolites have anyway been reported in living patients, with variation up to 40-fold between individuals [80]. Although differences between acute and chronic users, and in those with or without renal impairment, might be expected, ranges for all these groups overlapped. It is difficult to see, therefore, that deductions from morphine metabolite ratios in post-mortem samples can be made with any certainty.

Animal experiments have also been made to examine the effects of lipophilicity in determining redistribution of three β -adrenoceptor antagonists in rabbits [81]. For some drugs, such as moclobemide, animal experiments suggest

that little redistribution takes place [82]. Such experiments usually consider only a small number of animals, doses and time-points, and this, taken with the anatomical and pharmacological differences between species, makes it difficult to extrapolate the results to human cases.

Can the extent of post-mortem redistribution be deduced from the properties of a drug?

Leikin and Watson's review [8] tabulates approximate C : P ratios, where central concentrations were measured in heart blood. The authors, following Hilberg [83], suggest that drugs with a volume of distribution $>3 \text{ l kg}^{-1}$ are candidates for redistribution. The authors do not indicate uncertainty around the estimates of C : P ratio, which is undoubtedly very large. For example, a study of post-mortem concentrations of the opiate analgesic fentanyl has reported heart and femoral blood concentrations in 11 cases. The C : P ratio ranged from 0.89 to 3.2 (mean 1.6) [84]. However, the approximate figures can be used as a basis for testing this and other suggested relationships between the pharmacokinetic properties of a drug and its propensity to undergo post-mortem redistribution.

The relationship between C : P ratio and volume of distribution for the drugs listed by Leikin and Watson is weak (Figure 1): although most drugs that undergo redistribution, as judged by a C : P ratio >3.0 , have large volumes of distribution, there are several outlying drugs with large volumes of distribution that appear to undergo little or no redistribution. Other authors have already noted that volume of distribution cannot be the sole determinant of the extent of redistribution [81]. The C : P ratio exceeds the volume of distribution in l kg^{-1} for 15/33 drugs for which data were available, so the volume of distribution is not

an indication of the upper limit for divergence between ante-mortem and post-mortem samples. Likewise, there is no obvious relationship between the C : P ratio and the octanol : water partition coefficient (Figure 2).

Making deduction from post-mortem drug concentrations

The general problem is to decide whether a post-mortem concentration indicates that the deceased died from the action of the drug, or whether the drug was present incidentally. The problem is most straightforward where only one drug is involved and its post-mortem redistribution is negligible, so that concentrations are similar if measured in samples taken from different sites or at different times. For most, if not all drugs, that is unlikely. The difficulties can be eased by careful sampling [31, 85], even though intrinsic uncertainties in post-mortem analysis mean that compliance with the recommendations does not guarantee reliability. Early compilations of 'fatal' concentrations [33–36] did not specify sampling site, even though it was well recognized that for some drugs concentrations in solid organs differed greatly from those in 'blood' [86]. Druid and Holmgren addressed this by compiling a table of post-mortem concentrations of femoral venous blood, based on their set of Swedish data [87]. An elaboration, quoting 10th and 90th centiles of femoral blood concentrations of antidepressant drugs in fatal cases, has been published [88].

Good information on the rate of change of drug concentration with time could help, but there is likely to be substantial variability due to uncontrolled factors such as temperature and microbial action. Even if there is little or

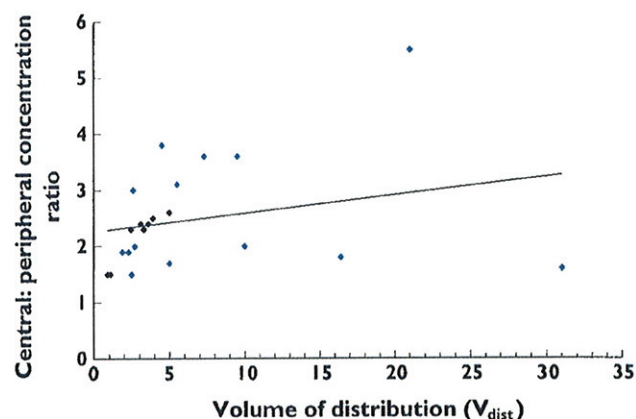


Figure 1

The relationship between the extent of post-mortem redistribution and the volume of distribution. The extent of post-mortem distribution is measured by the central : peripheral concentration ratio, taken from reference [8]. The volume of distribution is taken from [64]. The regression coefficient, $r = 0.247$, $P > 0.1$

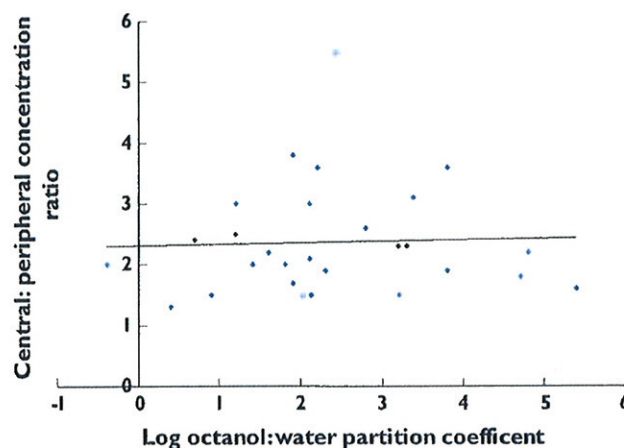
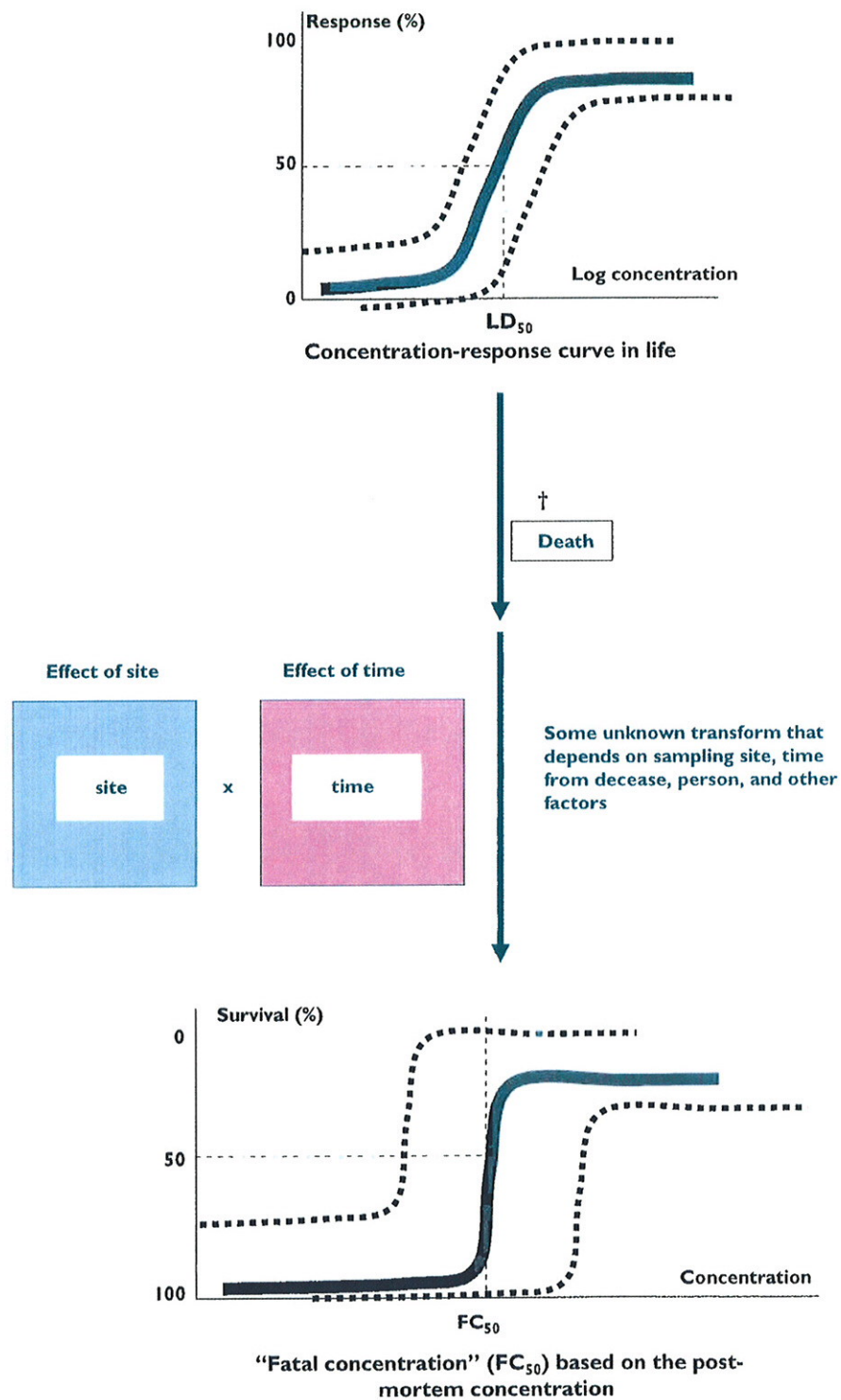


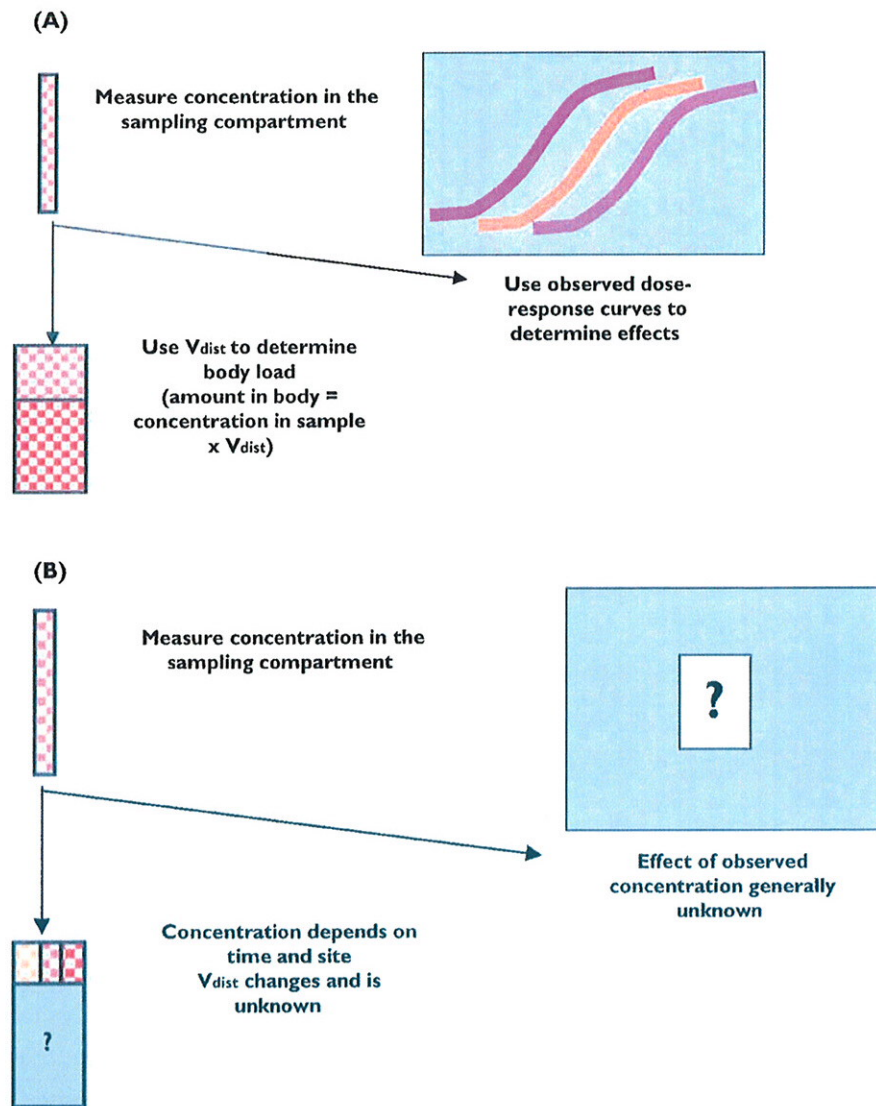
Figure 2

The relationship between the extent of post-mortem redistribution and log octanol : water partition coefficient. The extent of post-mortem distribution is measured by the central : peripheral concentration ratio, taken from reference [8]. The octanol : water partition coefficient is taken from [65]. The regression coefficient, $r = 0.035$, $P > 0.1$

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**Figure 3**

A scheme of the relationship between ante-mortem dose-response curve for a lethal drug and the definition of lethal concentration by reference to the observed post-mortem concentration

**Figure 4**

(a) Deductions made from concentrations of drug measured during life. If the relationship between concentration (or dose) and effect is known, then in some circumstances the likely effect can be deduced. Even in life, there are difficulties with drugs, such as ethanol, where responses are very variable; opiates, whose dose-response curve is substantially altered by repeated dosing; and penicillin, where a subset of patients is hypersusceptible to adverse effects. (b) Deductions made from concentrations of drug measured after death. It is now impossible to establish the administered dose, and the effect of a measured concentration cannot be deduced from dose-response curves determined in living subjects

no post-mortem redistribution, and there is a large series of cases in which a single drug has been taken, the problems of deciding whether the measured concentration indicates a drug-induced death (DID) or not (DID-not) are formidable. At its simplest, the problem is to define a concentration that, if found post mortem, indicates that a lethal concentration was present before death (Figure 3). Although the relationship between dose and response can be clear ante mortem (Figure 4a), any such relationship is likely to be clouded post mortem (Figure 4b). For the

answers to be reliable, a series of deaths in which the drug is detected has to be considered, and each death assigned to the DID or DID-not group without knowledge of the measured concentrations. That assignment, independent of concentration, is likely to be difficult. It might be possible if there were a characteristic and specific clinical picture, and if other competing causes of death could be excluded. Since, for example, most suicides are unobserved, the clinical picture in an individual death is often unknown. Since apparently healthy subjects may have

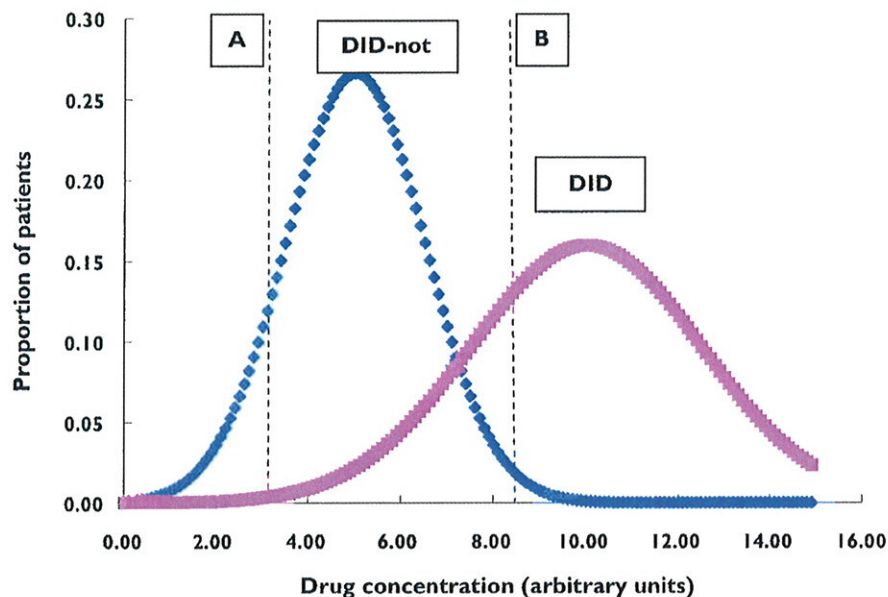


Figure 5

The proportion of patients having a specified post-mortem concentration of some hypothetical drug, and for two groups of subjects: those with drug-induced death (DID); and those with death not due to drugs (DID-not), allowing for likely variability between individuals. The two distributions may differ in shape, and may be skewed, but it is very likely that they will overlap considerably: those in whom concentration A was found may have died from the effects of the drug, whereas those in whom concentration B was found may not. There is no clear 'lethal concentration'

hidden causes of sudden death, notably cardiac arrhythmia [89], the exclusion of competing may itself be difficult.

Even if the deceased can be assigned to the DID and DID-not groups, it is very unlikely that drug concentrations in the two groups will be clearly separated (Figure 5). The overlap will partly result from biological variability in subjects and partly from sampling and analytical variability that will blur the distinction between samples of supposedly different concentrations. The biological variability may be extreme if the death is not due to poisoning, but, for example, to immunological effects, especially anaphylaxis: a concentration of penicillin that is much smaller than the conventional therapeutic concentration will nonetheless be lethal in a patient with severe Type I hypersensitivity. By contrast, doses of opioids that would be lethal in unexposed subjects are happily tolerated by heroin addicts whose receptors are downregulated by habitual exposure. Pharmacogenetic variation in the sensitivity of subjects to adverse effects may also prove to be important [90].

Conclusion

There is no reliable or obvious connection between concentrations measured in life and subsequent to death. Consequently, concentrations measured after death cannot generally be interpreted to yield concentrations present

before death. The definition of lethal concentrations is extremely difficult. For rigour, it is necessary to assign a series of deaths to the DID and DID-not categories independent of the drug concentrations, and examine how the concentrations differ between the two groups. Usually there will be a broad overlap, and a correspondingly wide range of uncertainty in deciding whether a concentration found after death caused the death. Post-mortem concentrations have been over-interpreted in the past, and good evidence should be required before 'lethal concentrations' are defined in the future.

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NMS Workorder No:

08095896

NMS Control No:

10843208

Client ID No:

08-02797

SPECIMENS:

One gray top tube containing ~ 10 mL of peripheral blood, one clear vial containing ~ 14 mL of peripheral blood and two white plastic containers (one containing ~ 30 mL of urine and one containing ~ 32 g of liver) were received on 03/28/08.

EXAMINATION:

Analysis Requested - Panel 8092B - Autopsy Toxicology Therapeutic and Abused Drug Screen
Test No. 1615B - Digoxin

FINDINGS:

Blood

ETHYL ALCOHOL
(by Enzymatic Assay & Headspace GC)

48 mg/dL (BAC=0.048 % w/v)

DILTIAZEM
(by GC & GC/MS)

630 nanog/mL

DIGOXIN
(by LC-MS/MS)

3.6 nanog/mL

QUINIDINE/QUININE*
(by GC/MS)

Trace

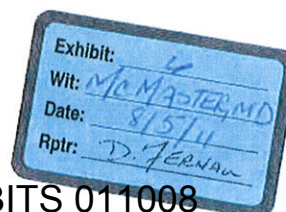
ATROPINE
(by GC/MS)

Positive

*Quinine and quinidine can be differentiated analytically, but this is a separate analysis. If further delineation is necessary, please contact the laboratory.

Incidental findings by GC/MS: CAFFEINE and THEOBROMINE.

Other than the above findings, examination of the specimens submitted did not reveal any positive findings of toxicological significance by procedures outlined in the accompanying Analysis Summary.



PLAINTIFFS' EXHIBITS 011008

08/05/2011 10:48 FAX 805 544 7427

McDaniel Reporters, Inc

001

**URGENT: DRUG RECALL****Digitek (digoxin tablets USP)**

April 28, 2008

Dear Valued Customer:

This is to inform you of a product recall involving:

Digitek® (digoxin tablets, USP)
NDC # 62794-145-01; 62794-145-10; 62794-145-56;
62794-146-01; 62794-146-10; 62794-146-56

See enclosed product labels (See Attachment 1).

This recall has been initiated due to overweight tablets. Potential risks to the patient depend upon the constituency of the tablets. Depending on the constituency of the tablets, double the dose is taken, it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy.

ACTAVIS has distributed the subject lots from 03/01/06 through 04/24/08. This recall should be carried out to the consumer level.

Upon receipt of this letter, please take the following action:

1. Immediately examine your inventory and quarantine and discontinue distribution of the affected lots.
2. In addition, if you may have further distributed the recalled product, please identify your retail-level customers and notify them at once of this product recall.
3. Additionally, if the retail-level customers have further distributed the recalled product, please identify the consumer and notify them immediately of this product recall.
4. Complete the enclosed form and mail it in the self-addressed, stamped envelope enclosed. To assure accountability, it is imperative that this form be returned even if you do not have product in stock or you have already returned the product.

Page 1 of 3

Exhibit:	7
Wit:	McDaniel
Date:	8/5/11
Rptr:	D. FERNAN

Confidential Subject to Protective Order

UDLL 000004008

08/05/2011 10:49 FAX 805 544 7427

McDaniel Reporters, Inc

002



URGENT: DRUG RECALL

Digitek (digoxin tablets, USP)

All product inventory is to be returned to:

Stericycle
2670 Executive Drive, Suite A
Indianapolis, IN 46241
RE: Digitek (Digoxin Tablets, USP)

A packing slip must be enclosed in the return, designating product, quantity and return shipping costs. Please use the enclosed labels on the material you are returning.

As soon as your return shipment of the referenced product is processed, a credit will be promptly issued for the value of the merchandise, plus shipping costs.

Sincerely,


Phyllis Cambridis

VP, US Quality and Compliance
Actavis, Inc.

Page 2 of 3

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UDLL 000004007

08/05/2011 10:49 FAX 805 544 7427

McDaniel Reporters, Inc

003

**URGENT: DRUG RECALL****Digitek (Digoxin Tablets, USP)****Business Reply Form**

Please complete this form and mail it in the enclosed, self-addressed, stamped envelope to:

Stericycle
2670 Executive Drive, Suite A
Indianapolis, IN 46241
Attention: RECALL COORDINATOR
RE: Digitek (Digoxin Tablets, USP)

Consignee Name and Address:

We have inspected our stock and:

☐ NO PRODUCT IS IN INVENTORY☐ WE ARE RETURNING THE FOLLOWING:

Lot Number	Number of Bottles

Page 1 of 3

Confidential Subject to Protective Order

UDLL 000004006